ABSTRACT

Introductory Statement

The drug to be used in this study is a human breast cancer cell line, called MDA-MB-231, that has been modified by insertion of a human gene called B7 (CD80). MDA-MB-231 was isolated from the pleural effusion of a 51 year old woman in 1974. The cell line was submitted to the Human Tumor Cell Bank of the ATCC after 14 passages and the ATCC seed stock after 24 serial subcultures. The cell line expresses the p185 gene product of Her2/neu and the HLA-A2 class I major histocompatibility complex allele. The unmodified cell line has been administered to patients previously in an attempt at vaccination (Clin Exp Immunol 39:90-6, 1980). We have modified the cell line by plasmid-mediated gene transfer of the cDNA for CD80 (costimulatory B7). The vector was transfected using lipofection.

The final vector used in our study, CMV-B7, was provided by Dr. Robert Fenton of the BRMP and is identical to the vector employed to generate the B7-transfected melanoma cells being used by Drs. Sznol and Fenton in their ongoing FDA and RAC-approved clinical trial, which has accrued 18 patients (personal communication). CMV-B7 was derived from BCMG Neo-B7 by removing all transforming sequences. CMV-B7 is transfected into malignant cells where it integrates into chromosomal DNA and is not capable of replication. Thus, the risk that the vector contains any transforming sequences, or that the host (patient's) cells could acquire any DNA containing transforming sequences is extremely small. The transfected cells will be lethally irradiated (10,000 cGy) before administration to patients.

General Investigational Plan

This application is submitted for approval to conduct a clinical trial to determine the feasibility of priming cytotoxic and helper T-cell immunity to specific tumor-associated antigens in women with metastatic breast cancer. We will determine the ability of a genetically-modified antigen-presenting breast cancer cell line in conjunction with GM-CSF as an adjuvant to induce specific immune response(s) in vivo. Immunologic studies will be performed on peripheral blood mononuclear cells and on lymphocytes removed from lymph nodes draining the primary tumor inoculation site. Gene-transfected cells are being used to ensure that the second co-stimulatory event required to activate specific T cells will be provided. Breast cancer cells express tumor antigens (e.g., her2/neu) but they lack costimulatory molecules like CD80 (B7). T-cell activation requires both signals. Thus, expression of CD80 on the breast cancer cell line should enhance the chances that an optimal activation signal will be delivered to the patient's T cells.

The study will be conducted in 30 women with metastatic breast cancer. They will be inoculated with the lethally-irradiated breast cancer cell line MDA-MB-231 modified to express human CD80 (B7.1; co-stimulatory signal) in conjunction with the adjuvant GM-CSF or BCG in the anterior right thigh. GM-CSF is being used to enhance endogenous antigen presenting cell function, perhaps via differentiation of dendritic cells. The contralateral thigh will receive no treatment or adjuvant alone. Approximately 10 days after tumor inoculation, the regional superficial lymph nodes draining the inoculation site (and the site of adjuvant injection on the contralateral side) will be removed surgically and tested for anti-tumor reactivity, and in particular, for activity specific for her2/neu. A total of five additional inoculations will be performed; however, additional lymph node harvests will not be performed. Instead, peripheral blood mononuclear cells will be studied for anti-her2/neu activity. Thirty patients divided into 6 cohorts will be treated with escalating doses of gene modified breast cancer cells, adjuvant, or both. The toxicity, efficacy, and immunologic effects of vaccination will be determined.

In summary, this translational study will determine the requirements and mechanisms for induction of tumor-specific immune function. This will be investigated by the administration of a tumor antigen-presenting cell (APC) capable of delivering the antigen-specific signal and the CD80-mediated costimulatory signal for complete T-cell activation. Furthermore, we will determine the influence of GM-CSF or BCG on the generation of antigen-specific tumor immunity.

Since BCG, GM-CSF and the MDA-MB-231 have all been administered to patients previously, we do not expect to see any new serious toxicities. Nonetheless, patients will be monitored closely for side effects, changes in immunologic function, and tumor regression.